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Combined therapy of mixed dyslipidemia in patients with high cardiovascular risk and changes in the lipid target values and atherogenic index of plasma

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ABSTRACT

Purpose: To evaluate the safety and efficacy of combined lipid-modifying agents (statin + fenofibrate) on plasma lipid profile including the atherogenic index of plasma (AIP = log [TG/HDL-C]) in patients at high and very high cardiovascular (CV) risk and mixed dyslipidemia.

Method: A total of 81 patients (53 males, 28 females; 60 ± 9.8 years) were included. Mixed dyslipidemia was defined as having 2 of the following 3 lipid abnormalities: LDL-cholesterol (C) >2.5 mmol/l, HDL-C <1.0 mmol/l in males and <1.3 mmol/l in females, triglycerides (TG) >1.7 mmol/l. Global CV risk was estimated according to the current European guidelines. Management with fenofibrate (160–267 mg) + atorvastatin (10–20 mg) or simvastatin (20–40 mg) was indicated for 6 months. Males and females were stratified according to the AIP risk categories: AIP <0.11 (low risk), AIP >0.21 (high risk).

Results: About 3/4 of high or very high CV risk patients with mixed dyslipidemia ($n = 81$) suffer from impaired glucose metabolism (44% had type 2 diabetes, 30% had impaired fasting glucose). Six-months combined therapy reduced LDL-C (by 29%) and TG (by 40%) significantly, but the increase of HDL-C (by 3%) was not significant. There were 47% of males and 57% of females who achieved the target LDL-C levels (<25 or <1.8 mmol/l) and 14% of males and 37% of females who received non-HDL-C <2.6 mmol/l at the end of the study. Also AIP

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was decreased significantly in majority of the patients (high risk AIP decreased from 87% to 47% of males and from 71% to 25% of females).

Conclusion: The combined lipid-modifying therapy led to a significant improvement of the plasma lipid profile, particularly of LDL-C, TG, non-HDL-C and AIP. Atherogenic index of plasma seems to be a very useful marker of CV risk in high and very high CV risk patients with mixed dyslipidemia and glucose abnormalities. More intensive management is needed in those patients.

Introduction

Patients with established atherosclerotic vascular diseases (e.g. myocardial infarction, stroke, chronic coronary heart disease, peripheral artery occlusive disease etc.) or subjects with documented cardiovascular disease (CVD) by invasive or non-invasive testing, patients with diabetes mellitus (DM) and one or more CV risk factors and/or target organ damage, patients with severe chronic kidney disease or subjects in primary prevention of CVD having an absolute risk of fatal CV events ≥10% according to the SCORE risk chart are considered as patients at very high CV risk. Patients with DM without any CV risk factors or target organ damage, patients with moderate chronic kidney disease, markedly elevated risk factors or global CV risk ≥5% and <10% in primary CVD prevention are considered as patients at high CV risk. All these very high or high-risk patients need to be motivated to modify their lifestyle (primarily to quit smoking, to have a healthy diet, exercise regularly and reduce stress) as well as initiate pharmacological therapy of conventional risk factors. Target values of blood pressure below 140/90 or around 130/80 mm Hg (with individual approach) and LDL-cholesterol (C) <2.5 mmol/l for patients at high CV risk and LDL-C <1.8 mmol/l or reduction of LDL-C ≥50% in very high-risk patients. Obesity and diabetes require intensive treatment [1]. According to the European Guidelines for the management of dyslipidemias (2011), which were accepted by the Czech Society of Atherosclerosis, the other lipid fractions should be tested in high-risk or very high-risk patients [2]. Mixed dyslipidemia described by elevated TG plus reduced HDL-C concentration is called atherogenic dyslipidemia. This dyslipidemia associates with insulin resistance and belongs to the cluster of the metabolic syndrome and also to type 2 DM frequently. Atherogenic dyslipidemia is considered as a main source of residual vascular risk in patients, who have aimed the target values of LDL-C due to statin therapy in most cases. Even though the PROCAM study has proven that an elevated TG level increases CVD risk independently of the level of LDL-C [3], the European Guidelines do not mention either plasma TG or HDL-C as primary treatment aims, even for those patients suffering from dyslipidemia with a high CV risk. To achieve optimal levels of fasting plasma TG <1.7 mmol/l and HDL-C >1.3 mmol/l in women and >1.0 mmol/l in men can be considered as secondary or optional aims especially in patients with metabolic syndrome and/or type 2 DM [2]. Both the National Cholesterol Education Program (NCEP) III and the European Guidelines recommend to count and reduce non-HDL-C to <3.3 mmol/l and apolipoprotein B (Apo-B) <0.9 g/l for patients with elevated TG and moderate CV risk [4]. In patients with type 2 diabetes and very high CV risk, who have achieved recommended goal for LDL-C <1.8 mmol/l, to reduce non-HDL-C <2.6 and Apo-B <0.8 g/l represent the secondary targets.

Some years ago, Dobiasova and Frohlich proposed an atherogenic index of plasma (AIP = log[TG/HDL-C]) that takes into account the importance of plasma concentrations of TG and HDL-C, which is based on laboratory findings concerning the mechanism of regulation of the size of lipoproteins in the general population [5,6]. It demonstrates that a logarithmic transformation of the molar concentrations of TG and HDL-C is closely related to the sizes of HDL-C, LDL-C and VLDL-C particles, which are now considered to be new-generation indicators of CV risk and define the atherogenic genotype of plasma more precisely than classical biochemical indicators total cholesterol, LDL-C, HDL-C, TG, Apo-A, Apo-B, etc. However, these tests are time-consuming and are expensive and the result cannot be expressed as a single number, but AIP can be used for monitoring of actual lipoprotein profile and predicting CV risk [7,8].

In this study, we focused on patients with mixed dyslipidemia and high or very high CV risk, for whom we treated with a combination of statin and fenofibrate. The objective of the study was to evaluate the safety and efficacy of this combined therapy on individual components of the lipid spectrum, including AIP.

Method

The study took place some years ago in 6 lipid outpatient clinics: at the 2nd Medical Department of the University Hospital in Pilsen, Department of Clinical Biochemistry of the St Anna University Hospital in Brno, the 3rd Medical Department of the University Hospital in Prague, the Diabetology Center of the Prague Institute for Clinical and Experimental Medicine, the 2nd Medical Department of the St Anna University Hospital in Brno, Department of Metabolic Care and Gerontology of the University Hospital in Hradec Kralove. Patients were recruited if they met 2 inclusion criteria: firstly, patients at high or very high CV risk according to the current guidelines mentioned above [2]. Secondly, patients with untreated mixed dyslipidemia or treated with statin or fibrate monotherapy defined as having 2 of the following 3 lipid abnormalities: LDL-C >2.5 mmol/l, HDL-C <1.0 mmol/l in

males and <1.3 mmol/l in females and TG >1.7 mmol/l. The exclusion criteria of our study included current treatment with combined lipid-lowering drugs, familiar hypercholesterolemia treated with high doses of statins (atorvastatin >20 mg or simvastatin >40 mg), an acute CV event during the last 3 months, BMI ≥40 kg/m^2, the presence of fatal diseases, non-adherence to treatment, serious psychiatric illnesses, ALT or AST values >3-fold greater than the upper normal level, creatine kinase (CK) >5-fold greater than the upper normal level or myopathy in the patient history, creatinine levels >150 μmol/l, glycosylated hemoglobin HbA_{1C} >65 mmol/mol (IFCC), disorder of the thyroid gland (hypo- or hyperthyreosis), insulin-treated diabetes, women of working age with positive pregnancy test. All patients gave written informed consent before entering the study.

The study included 3 visits (I, II and III) to the hospital at intervals of 3 months and 12 h fasting blood samples were taken at each visit. At visit I, the start of the study, the patient was reminded of the importance of a healthy lifestyle and intervention was initiated for risk factors the patient had not changed and health educational materials were given to the patient. A combination therapy was administered to all patients. Patients not already receiving a lipid-lowering drug were given fenofibrate (160 mg) + atorvastatin (10 mg) or simvastatin (20 mg). For patients receiving any dose of fibrate, fibrate was replaced by fenofibrate (160 mg) + atorvastatin (10 mg) or simvastatin (20 mg). For patients receiving statin in any acceptable dosage, the dose was adjusted to atorvastatin (10 mg) or simvastatin (20 mg) + fenofibrate (160 mg). Patients attended for visit II after 3 months of combination therapy and a complete control lipidogram was made. If LDL-C <2.5 in high-risk or <1.8 mmol/l in very high-risk patients were not achieved, the dose of statin was increased (simvastatin to 40 mg or atorvastatin to 20 mg). For patients who did not achieve the optimal values of TG <1.7 mmol/l or HDL-C ≥1.0 mmo/l in males or HDL-C ≥1.3 mmol/l in females, the daily dose of fenofibrate was increased to 267 mg. At visit III, the participating physician decided whether the patient would continue with the medication (if the patient achieved target lipid values) or the therapy was adjusted as needed. The patient was asked to recall all potentially adverse side effects during the duration of the study and these were recorded.

We used the AIP (AIP = log[TG/HDL-C]) to evaluate the CV risk for each patient [6]. AIP <0.11 was classified as low CV risk; AIP 0.1–0.21 was classified as moderate CV risk; and AIP >0.21 was classified as high CV risk [7,8].

Total cholesterol (TC), TG, HDL-C and other biochemical parameters were measured with an enzymatic autoanalyzer (Beckman Coulter AU 680, Beckman Coulter Inc., USA). LDL-C was calculated using the Friedewald formula and Apo-B and Apo-AI were measured by an immunoturbidimetric assay. These lipid parameters and the calculated values of non-HDL-C and AIP were expressed according to the non-parametric distribution as the medians and standard deviations of the quartiles. Statistical analysis of the variation of individual lipid parameters and AIP before the treatment started and 3 months later (visit II versus visit I), at 3 months and at 6 months following the initiation of the treatment (visit II versus visit III) and before initiation of the treatment and 6 months later (visit III versus visit I) was conducted using Friedman's test, which compares the values of medians. Decrease or increase in lipid values and AIP were expressed in absolute values and in percentages using the initial values as a base. The incidence of adverse events was evaluated by analysis of variance (ANOVA).

Results

The baseline data of 81 patients (53 males and 28 females) included in the study are given in Table 1: 78% (74% males and 86% females) met the criterion of high LDL-C; 96% (98% males and 96% females) met the criterion of high TG; and 49% (only 36% males and 75% females) of patients met the criterion of low HDL-C. About 44% of patients suffer from type 2 DM, 27% from atherosclerotic vascular disease (stable coronary heart disease or ischemic stroke) and 29% patients were at high or very high CV risk (≥5%). In more than half of non-diabetic patients (53%) was assessed impaired fasting glucose during the visit I, i.e. glucose level above 5.6 and below 7.0 mmol/l. It means, that about 3/4 of all included patients at high or very high CV risk had impaired glucose metabolism.

At visit II, the dose of statin was increased from 10 to 20 mg of atorvastatin or from 20 to 40 mg of simvastatin for the 8 (10%) patients who had not achieved LDL-C <2.5 (<1.8) mmol/l; the dose of fenofibrate was increased to 267 mg for the 26 (32%) patients who had not achieved TG <1.7 mmol/l or HDL-C was not above the target value. The dose of both medications needed to be increased in 32 (40%) patients and the doses of one or both lipid-modifying drugs were increased in a total of 66 (82%) patients. The lipid parameters after 3 months and after 6 months of combination therapy are given in Table 2. At the end of the study the level of plasma LDL-C was decreased

Table 1 – Baseline characteristics of the sample (53 men and 28 women) with mixed dyslipidemia and high cardiovascular risk.

Factor	Mean ± SD	Median (range)
Age (years)	59.6 ± 9.8	60 (34–83)
BMI (kg/m^2)	31.9 ± 22.5	29 (22–39)
Waist (cm)	100 ± 15	102 (64–116)
Systolic BP (mm Hg)	133 ± 12	134 (75–162)
Diastolic BP (mm Hg)	83 ± 8	81 (64–101)
Pulse (*n*/min)	70 ± 8	70 (52–91)
Total C (mmol/l)	5.92 ± 1.30	5.76 (3.40–12.25)
LDL-C (mmol/l)	3.45 ± 0.95	3. 41 (1.70–6.77)
HDL-C (mmol/l)	1.16 ± 0.27	1.14 (0.37–2.08)
Triglycerides (mmol/l)	3.61 ± 2.16	2.93 (1.50–12.53)
Apolipoprotein A (g/l)	1.33 ± 0.43	1.30 (0.89–2.37)
Apolipoprotein B (g/l)	1.13 ± 0.33	1.13 (0.52–1.77)
Fasting glycemia (mmol/l)	6.41 ± 1.50	5.95 (4.40–12.90)
HbA_{1C} (mmol/mol)	51 ± 8.2	49 (38–70)
ALT (μkat/l)	0.66 ± 0.84	0.56 (0.20–1.47)
AST (μkat/l)	0.49 ± 0.19	0.45 (0.21–1.82)
GMT (μkat/l)	0.78 ± 0.66	0.57 (0.16–4.11)
Creatine kinase (μkat/l)	2.1 ± 1.7	1.7 (0.6–13.2)

SD, standard deviation; BMI, body mass index; C, cholesterol; HbA_{1C}, glycosylated hemoglobin; ALT, alanineaminotransferase; AST, aspartate aminotransferase; GMT, gamma glutamyltransferase.

Table 2 – Changes in plasma LDL-C, HDL-C, triglycerides, apolipoprotein B and non-HDL-C (medians).

	Visit			p (Friedman test)		
	I	II	III	I–II	II–III	I–III
LDL-C (mmol/l)	3.41	2.79	2.53	***		***
HDL-C (mmol/l)	1.14	1.14	1.16			
Triglycerides (mmol/l)	2.93	2.10	1.78	***	***	***
Apolipoprotein B (g/l)	1.13	0.96	0.83	***		***
Non-HDL-C (mmol/l)	4.63	3.75	3.46	***		***

LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; Visit I, baseline visit before treatment; visit II, after treatment for 3 months; visit III, after treatment for 6 months (the end of the study).
*** $p < 0.001$.

Table 3 – Changes in AIP after 3 months and after 6 months of combination therapy.

Patients	AIP median (quartile deviations)			(Friedman test) p		
	Visit I	Visit II	Visit III	I–II	II–III	I–III
Men	0.459 (0.198; 1.184)	0.334 (−0.193; 0.871)	0.251 (−0.290; 0.856)	0.001	0.01	0.001
Women	0.332 (−0.006; 1.490)	0.139 (−0.511; 0.758)	0.049 (−0.428; 0.725)	0.001	NS	0.001
Total	0.415 (−0.006; 1.490)	0.248 (−0.511; 0.871)	0.206 (−0.428; 0.856)	0.001	0.01	0.001

AIP, atherogenic index of plasma [log(TG/HDL-C)]; visit I, baseline visit before treatment; visit II, after treatment for 3 months; visit III, after treatment for 6 months (the end of the study).

Table 4 – Target LDL-C, HDL-C, TG,. AIP values, apo B and non-HDL-C in 53 men and 28 women before treatment and after 6 months of combination therapy.

Target lipid values	Before treatment n (%)		After treatment n (%)	
	Men	Women	Men	Women
LDL-C < 2.5 (mmol/l)	8 (15)	4 (14)	25 (47)	16 (57)
HDL-C* (mmol/l)	34 (64)	7 (25)	44 (83)	11 (39)
TG < 1.7 (mmol/l)	1 (2)	1 (4)	22 (42)	18 (64)
#AIP < 0.10	0 (0)	3 (11)	18 (34)	16 (61)
##AIP > 0.21	46 (87)	20 (71)	25 (47)	7 (25)
Apo B < 0.8 (g/l)	2 (5)	4 (17)	13 (30)	11 (48)
Non-HDL-C < 2.6 (mmol/l)	1 (2)	0	7 (14)	10 (37)

LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol; TG, triglycerides; AIP, atherogenic index of plasma [log (TG/HDL-C)]. Apo B, apolipopotein B; Non-HDL-C = total C minus HDL-C.
* HDL-C men > 1.0 mmol/l, women > 1.3 mmol/l.
# AIP < 0.10 low risk.
AIP > 0.21 high risk.

significantly ($p < 0.001$) by 29% and HDL-C was increased by only 3% (not significant), TG was decreased significantly ($p < 0.001$) by 40%, the level of Apo-B was decreased significantly ($p < 0.001$) by 27%, and non HDL-C was decreased significantly ($p < 0.001$) by 25%.

During the entire course of the therapy, AIP was decreased significantly ($p < 0.001$) in the majority of patients receiving combination therapy (Table 3). The mean value was decreased by approximately half in males and to a greater extent in females; AIP was unchanged in 8 (15%) males and in 2 (7%) females. The proportion of patients at low risk AIP increased from zero to 34% of males and from 11% to 61% of females during the course of the treatment; conversely the number of patients at high risk AIP decreased from 87% to 47% of males and from 71% to 25% of females.

Table 4 gives the numbers of males and females with target lipid values and in the low risk AIP category before treatment and those who achieved target lipid values and the low risk AIP category after 6 months of combination therapy with statin and fibrate. At the end of the study, the target level of LDL-C <2.5 mmol/l [1,8] was achieved by 47% of males and 57% of females. HDL-C >1.0 mmol/l was achieved by 83% of males and >1.3 mmol/l by 39% of females. Plasma TG <1.7 mmol/l was achieved by 42% of males and by 64% of females. The target value of non-HDL-C <2.6 mmol/l and apo-B <0.8 g/l was achieved by 14% and 30% of males respectively and by 37% and 48% of females respectively.

The few adverse effects associated with statin + fenofibrate therapy are given in Table 5. One patient entered the study with a slightly elevated level of creatinine kinase

Table 5 – Adverse effects of combination therapy.

	Visit I	Visit II	Visit III	*p*
Muscle weakness	0	2	2	NS
Muscle pain	0	2	3	NS
Hair loss	0	1	2	NS
Fatigue	0	3	1	NS
Overall weakness	0	3	0	NS
Nausea	0	1	1	NS

Visit I, baseline visit before treatment; visit II, after treatment for 3 months; visit III, after treatment for 6 months (the end of the study); NS, not significant.

(CK = 13.2 μkat/l), which did not change significantly throughout the study.

Discussion

About 3/4 of high or very high CV risk patients with mixed dyslipidemia ($n = 81$) suffer from impaired glucose metabolism: 44% had type 2 DM and 30% had impaired fasting glucose. The low dose of lipid-modifying agents had to be increased in most patients (82% of the sample) after the 3 months therapy: statins in 10% of patients, fibrates in 32% of patients and both drugs in 40% of patients. It was found, that administration of combined therapy with statin + fenofibrate for 6 months significantly reduced levels of LDL-C (by 29%) and TG (by 40%), but the increase in the level of HDL-C (by 3%) was not significant. There were 47% of males and 57% of females who achieved the recommended LDL-C levels (<2.5 or <1.8 mmol/l) and 14% of males and 37% of females who received non-HDL-C <2.6 mmol/l at the end of the study. Also AIP was decreased significantly in the majority of patients following combined lipid-modifying therapy during the course of the study. Low risk AIP was achieved in 34% of males and in 61% of females. That was why the lipid-modifying therapy had to be intensified in the majority of patients at the end of the study.

Even though 82% of patients were given increased doses of lipid-modifying agents, the tolerance of combined treatment was excellent. There was no occurrence of a serious adverse event; i.e. there was no rhabdomyolysis, but muscle pain and weakness were temporary and not associated with an increase of enzymes specific to myopathy. It is in agreement with the previous large lipid-modifying trials FIELD (The Fenofibrate Intervention and Event Lowering in Diabetes) and ACCORD (The Action to Control Cardiovascular Risk in Diabetes), both of them have confirmed, that treatment of thousands of diabetic patients with a combination of simvastatin and fenofibrate was very well tolerated and safe [9,10].

Furthermore, the effectiveness and tolerability of simvastatin plus fenofibrate for combined hyperlipidemia (SAFARI) trial proved the same effects [11]. In that study, which randomized 619 patients on simvastatin monotherapy (20 mg) or simvastatin (20 mg) + fenofibrate (160 mg) combination therapy, there was no incidence of rhabdomyolysis or clinical myopathy. Nevertheless, after 12 months of treatment combination therapy was more effective in reducing TG (24% reduction) and LDL-C (6% additional reduction) and increasing HDL-C (by an additional 9%) than statin monotherapy. The results of our study concur with many findings of the SAFARI trial in the decrease of LDL-C and TG levels. Only the increase in HDL-C was greater in the SAFARI study (mean 19% increase) than in our study (mean 3% increase). This can be explained by the fact that the patients in our trial had higher HDL-C levels at baseline (mean 1.18 mmol/l) than those in the SAFARI trial (mean 1.13 mmol/l), thus the effect of combined therapy was less pronounced. It is known from the SAFARI study that combination therapy increased the size of individual LDL particles, which formed less dense and less atherogenic particles. We expect that this change in LDL particle size occurred in our study because of the reduction in plasma TG levels and decrease of AIP.

Atherogenic index of plasma (AIP = log[TG/HDL-C]) reflects not only the balance between risk and protective lipoproteins, but also correlates with lipoprotein particle size and cholesterol esterification rate [12,13]. It seems to be very important for the patients with mixed dyslipidemia, esp. in patients with atherogenic dyslipidemia, in evaluation residual vascular risk in patients with achieved LDL-C goal [14]. Reaven's group published a study, in which they observed, that the TG/HDL-C ratio is closely related to insulin resistance expressed as increased levels of fasting insulin in a sample of overweight individuals [15]. A TG/HDL-C ratio of 3 mg/dl was considered borderline for the prediction of the presence of small dense LDL particles in a Caucasian population. According to the authors, this ratio could provide clinicians with a new marker for hyperinsulinemia in patients of normal weight [16]. The relationship between plasma insulin and fraction esterification rate (FER_{HDL}) as well as between AIP and hyperinsulinemia was reported by Dobiasova and Frohlich much earlier [1998], than it was described by Reaven et al. [17].

There is not recommended any target level of TGs in the European Guidelines, but TGs are an important regulator of lipid metabolism and atherogenesis. An increased concentration of TGs is associated with a high concentration of atherogenic HDL, LDL and VLDL particles and an increased transport of cholesterol esters from HDL particles to lipoprotein containing Apo-B [12,18,19]. The ACCORD lipid trial showed that treatment with fibrates should be considered as beneficial for patients with type 2 DM treated by statins who also have atherogenic dyslipidemia, defined as TG ≥2.3 mmol/l and HDL-C ≤0.9 mmol/l. Combined lipid-lowering therapy (simvastatin + fenofibrate) has significantly reduced the prevalence of macrovascular complications (myocardial infarction, stroke and cardiovascular mortality) [20]. Diabetics without atherogenic dyslipidemia had no benefit from the combined lipid-lowering therapy with regard to the prevention of macrovascular complications, but it reduced the progression of microvascular complications [10].

In our study, the target levels of lipids were not achieved in all patients despite an increase in the doses of statins and fenofibrate at visit II, after 3 subsequent months of combination therapy. The LDL-C target was not achieved by 53% of males and 43% of females; that is why higher doses of statin are needed for high and especially for very high risk patients than the used. The TG optimal level was not reached by 58% of males and 36% of females; and the HDL-C optimal level was not reached by 17% of males and 61% of females; and 47% of males and 25% of females remained at high-risk AIP. These

data showed that low HDL-C syndrome was found more frequently in women (HDL-C <1.3 mmol/l was found in 75% of females and values of <1.0 mmol/l were found in 36% of males). Combination therapy increased HDL-C levels to above the target values in 19% of males and 14% of females. Recommended target value of Apo-B <0.8 g/l and non-HDL-C were achieved in 30% and 14% of males respectively and in 48% and 37% of females respectively. These results suggest that very high risk patients need strong implementation of non-pharmacological recommendations (low-fat diet, regular physical activity, non-smoking) and also more intensive lipid-lowering therapy, especially high dose of statins or more effective statin (such as rosuvastatin) to achieve recommended LDL-C values. To achieve the recommended values of non-HDL-C and Apo-B in patients with high CV risk and mixed dyslipidemia, higher dose of fenofibrate and/or another combination of lipid-modifying drugs would be useful; e.g. statin + ezetimibe, fibrate + ezetimibe or statin + fibrate + ezetimibe. The impact of combined lipid-modifying therapy including ezetimibe on CVD morbidity and mortality need to be proved, although smaller clinical studies have shown very good effects not only on lipid metabolism but also on the other risk factors in various patient groups [21,22]. Advised combined therapy with nicotinic acid (niacin) is not possible in Czech Republic, because the fixed combination of niacin with laropiprante (Tredaptiv) was removed from the drug register, and separate niacin has not been registered anyway. New lipid-modifying agents are on the way.

Conclusion

Combination therapy by statin and fenofibrate in patients at high or very high CV risk (majority of them had type 2 DM or impaired fasting glucose) and mixed dyslipidemia [defined as the presence of 2 out of 3 pathological lipid parameter levels: TG >1.7 mmol/l, LDL-C ≥2.5 [1,8] mmol/l, HDL-C <1.0 in males and <1.3 mmol/l in females], was relatively effective and well tolerated. It led to a significant reduction in AIP (50% reduction compared to baseline) as a surrogate of CV risk associated with mixed dyslipidemia and insulin resistance. It is expected that a combined lipid-modifying treatment could have a protective effect regarding the incidence of CV disease and their mortality, especially in patients at high and very high CV risk and glucose metabolism abnormalities.

Not only primary goal, i.e. LDL-C targets (<2.5 or <1.8 mmol/l), but also optimal values of TG (<1.7 mmol/l) and HDL-C (>1.0 mmol/l in males and >1.3 mmol/l in females) controlled by non-HDL-C (<2.6 mmol/l) or Apo-B levels (<0.8 g/l) are recommended as a secondary goals of treatment in patients with elevated TGs level according to the contemporary guidelines. Atherogenic index of plasma used in our study seems to be one of the important markers of atherogenic risk in patients with mixed dyslipidemia, especially in patients with atherogenic dyslipidemia (elevated TG and reduced HDL-C), frequently occurring in type 2 diabetics or in patients with insulin resistance or metabolic syndrome. The logarithmic transformation of the molar concentrations of TG and HDL-C is closely related to the size of HDL-C, LDL-C and VLDL-C particles, which are considered to be new-generation indicators of CV risk and define the atherogenic genotype of plasma more precisely than classical biochemical indicators. More intensive therapy is needed in patients at high and very high CV risk and mixed dyslipidemia; trends to the combination of 2 or 3 lipid-modifying agents seem to be very useful in short future.

Conflict of interest

No conflict of interest.

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Ethical statement

We state that the research was done according to ethical standards.

Informed consent

All patients agreed to participate in the research.

All the patients gave an informed consent. We have an ethics committee approval.

All these data are kept in paper in our center.

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